



Status

Active

Medical and Behavioral Health Policy

Section: Medicine

Policy Number: II-158

Effective Date: 01/20/2014

Blue Cross and Blue Shield of Minnesota medical policies do not imply that members should not receive specific services based on the recommendation of their provider. These policies govern coverage and not clinical practice. Providers are responsible for medical advice and treatment of patients. Members with specific health care needs should consult an appropriate health care professional.

INTRAVENOUS HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2) TARGETED AGENTS

Description: Activation and dimerization of the human epidermal growth factor receptor 2 (*HER2*) gene cause alterations in several complex downstream-signaling cascades that are involved in regulation of cell growth, proliferation, migration, adhesion, and survival, and thus has been implicated in oncogenesis.

The *HER2* gene is amplified and HER2 protein overexpressed in approximately 20% of breast cancers. HER2 overexpression in breast cancer is associated with more aggressive disease and higher relapse and mortality rates. HER2 is also overexpressed in other cancers.

Trastuzumab (Herceptin[®]) is a monoclonal antibody that acts as a HER2 receptor antagonist. It has been approved by the FDA for the following indications:

- Adjuvant treatment of HER2 overexpressing breast cancer;
- Treatment of HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma in combination with cisplatin and capecitabine or 5-fluorouracil.

Pertuzumab (Perjeta[™]) is a monoclonal antibody developed to target a different part of the HER2 protein than trastuzumab with the goal of further reducing growth of HER2-positive breast cancers. It is FDA approved for use in combination with trastuzumab and docetaxel:

- For the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease; and
- As neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.

Ado-trastuzumab emtansine (Kadcyla[™]) is a HER2 targeted antibody-

drug conjugate of trastuzumab and a microtubule inhibitor. Ado-trastuzumab emtansine disrupts microtubule networks in the cell which results in cell cycle arrest and apoptotic cell death.

Kadcyla has been approved by the FDA as a single agent for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane separately or in combination. Patients should have either received prior therapy for metastatic disease or developed recurrence during or within 6 months of completing adjuvant therapy.

HER2 Testing

Appropriate patient selection for trastuzumab therapy is predicated on detection of HER2 overexpression. The American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP) issued joint guideline recommendations for HER2 testing in breast cancer (<http://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2013-0953-SA>). The recommendations state that HER2 overexpression should be assessed only by facilities with demonstrated proficiency in the specific assay being used. Unreliable results may result from improper assay performance.

Recommendations on HER2 assessment from ASCO/CAP apply only to breast cancer. Protocols for assessment of HER2 in gastric, esophageal and gastroesophageal junction adenocarcinoma are available through the National Comprehensive Cancer Network[®] (NCCN) guidelines on gastric cancer (http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf) and esophageal and esophagogastric junction cancers (http://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf). Guidelines are available with registration.

U.S. Food and Drug Administration (FDA)-approved tests for HER2 overexpression include the PathVysion HER-2 DNA Probe Kit (Abbott Molecular) INFORM HER2 Dual ISH DNA Probe Cocktail (Ventana Medical Systems, Inc.), Bond Oracle HER2 IHC System (Leica Biosystems), HercepTest™ (DAKO USA), HER2 FISH Pharmdx™ Kit and the HER2 CISH Pharmdx™ Kit (Dako Denmark A/S), SPOT-Light® HER2 CISH™ Kit (Invitrogen Corporation).

Other testing methodologies have been proposed. An example is the HERmark[®] Breast Cancer Assay which quantitatively measures total HER2 protein expression and homodimers.

Definitions:

Dimer: Molecule made up of two simpler identical molecules. Dimerization is the process by which these two simpler molecules form a larger molecule.

Gene expression refers to the process by which the information encoded in a gene is used to direct the assembly of gene products (usually proteins). If a gene is overexpressed in cells an excess of

gene product is produced, which in turn can affect regulation of cell growth, proliferation, and survival.

HER2 positive cancer indicates that the HER2 protein is overexpressed through immunohistochemical (IHC) assay testing or there are excess copies of the *HER2* gene in tumor tissue as detected by in situ hybridization (ISH).

Immunohistochemical (IHC) assay: In IHC, tissue is treated with antibodies that bind the specific molecule. These are made visible under a microscope by using a color reaction with a chemical or with radioactive material introduced to the tissue.

In situ hybridization (ISH) assay: Segments of DNA or RNA that contain a fluorescent dye (fluorescence in situ hybridization or FISH) or specific reagents are added to cells in a sample. When these segments of DNA bind to specific genes or areas of chromosomes they fluoresce or produce reactions that can be viewed under a microscope equipped with a special light. ISH assays are used to evaluate gene amplification or deletion as well as the number and translocations of chromosomes.

Monoclonal antibody: A protein developed in the laboratory that can locate and bind to specific substances in the body and on the surface of cancer cells.

Policy:

I. Breast Cancer

- A. Trastuzumab (Herceptin), ado-trastuzumab emtansine (Kadcyla), and pertuzumab (Perjeta) may be considered **MEDICALLY NECESSARY** for treatment of patients with breast cancer only when tumor overexpression of HER2 has been confirmed by testing in accordance with current ASCO/CAP or NCCN guidelines.
- B. Trastuzumab (Herceptin), ado-trastuzumab emtansine (Kadcyla), and pertuzumab (Perjeta) are considered **INVESTIGATIVE** for treatment of breast cancer for which tumor overexpression of HER2 has not been confirmed.

II. Gastric, Esophageal, and Gastroesophageal Junction Adenocarcinoma

- A. Trastuzumab (Herceptin) may be considered **MEDICALLY NECESSARY** for treatment of patients when tumor overexpression of HER2 has been confirmed by testing in accordance with current ASCO/CAP or NCCN guidelines in the following instances:
 - 1. Metastatic gastric or gastroesophageal junction adenocarcinoma;
OR
 - 2. Palliative care of patients with advanced gastric, esophageal or gastroesophageal junction adenocarcinoma with a Karnofsky performance score of 60% or greater

(Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed, or able to carry on normal activity and to work; no special care needed) OR Eastern Cooperative Oncology Group (ECOG) performance score of 2 or less in combination with systemic chemotherapy. An ECOG score of 2 or less indicates that the patient is ambulatory more than 50% of waking hours and capable of self-care.

- B. Trastuzumab (Herceptin) is considered **INVESTIGATIVE** for treatment of advanced or metastatic gastric, esophageal or gastroesophageal junction adenocarcinoma for which tumor overexpression of HER2 has not been confirmed.
- C. Ado-trastuzumab emtansine (Kadcyla) and pertuzumab (Perjeta) are considered **INVESTIGATIVE** for treatment of gastric, esophageal, or gastroesophageal junction adenocarcinoma.

III. Other Cancers

Trastuzumab (Herceptin), ado-trastuzumab emtansine (Kadcyla), and pertuzumab (Perjeta) are considered **INVESTIGATIVE** for treatment of all other cancers including but not limited to colorectal, endometrial, esophageal (except as stated in IIA above), gastric (except as stated in IIA above), head and neck, non-small cell lung, osteosarcoma, ovarian, pancreatic, peritoneal, prostate, salivary gland, and urothelial.

IV. Assessment of HER2 expression

Assessment of HER2 expression in tumor tissue that is not in accordance with current ASCO/CAP or NCCN guidelines, including but not limited to by quantitative total HER2 expression or HER2 homodimer measurement, is considered **INVESTIGATIVE**.

Coverage:

Blue Cross and Blue Shield of Minnesota medical policies apply generally to all Blue Cross and Blue Plus plans and products. Benefit plans vary in coverage and some plans may not provide coverage for certain services addressed in the medical policies.

Medicaid products and some self-insured plans may have additional policies and prior authorization requirements. Receipt of benefits is subject to all terms and conditions of the member's summary plan description (SPD). As applicable, review the provisions relating to a specific coverage determination, including exclusions and limitations. Blue Cross reserves the right to revise, update and/or add to its medical policies at any time without notice.

For Medicare NCD and/or Medicare LCD, please consult CMS or National Government Services websites.

Refer to the Pre-Certification/Pre-Authorization section of the Medical Behavioral Health Policy Manual for the full list of services,

procedures, prescription drugs, and medical devices that require Pre-certification/Pre-Authorization. Note that services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial of claims may result if criteria are not met.

Coding: *The following codes are included below for informational purposes only, and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.*

CPT:

88342 Immunohistochemistry (including tissue immunoperoxidase), each antibody

88360 Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, each antibody; manual

88361 Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, each antibody; using computer-assisted technology

88365 In situ hybridization (eg, FISH), each probe

88367 Morphometric analysis, in situ hybridization (quantitative or semi-quantitative) each probe; using computer-assisted technology

88368 Morphometric analysis, in situ hybridization (quantitative or semi-quantitative) each probe; manual

HCPCS:

J9306 Injection, pertuzumab, 1 mg

J9354 Injection, ado-trastuzumab emtansine, 1 mg

J9355 Injection, trastuzumab, 10 mg

S3854 Gene expression profiling panel for use in the management of breast cancer treatment

Deleted Codes: C9131, C9292

Policy History: **Developed March 14, 2012**

Most recent history:

Revised September 12, 2012

Revised November 13, 2013

Cross Reference:

Current Procedural Terminology (CPT®) is copyright 2013 American Medical Association. All Rights Reserved. No fee schedules, basic units, relative values, or related listings are included in CPT. The AMA assumes no liability for the data contained

herein. Applicable FARS/DFARS restrictions apply to government use.

Copyright 2014 Blue Cross Blue Shield of Minnesota.

